REMARKS

This paper is filed in response to the Non-Final Office Action dated April 2, 2010. Claims 1-41, 44-49 are currently pending in this application, with only claims 1-15, 21-30, 36-40 and 44-49 being currently under examination. Reconsideration of the instant application is respectfully requested in view of the amendments above and the following remarks.

1. Rejections under 35 U.S.C § 103

The Examiner essentially repeats rejections presented in the Office Action mailed on April 22, 2009, and withdrawn in the Office Action mailed on July 14, 2009. The Examiner, however, does not present any new reasons for why the instant claims are obvious in light of the cited references. Accordingly, Applicants respectfully request withdrawal of this ground for rejection.

Claims 7-15, 24, 25, 36-40, 44, 45 and 47-49 were rejected under 35 U.S.C. § 103 as being unpatentable over Hair et al. (U.S. Patent 6,521,750) or (U.S. 6, 858,431) in view of Nagahara et al.

In the Office Action mailed on July 14, 2009, the Examiner stated as follows in regard to Hair et al:

> However, Hair et al. do not teach a method of inducing bone formation in a mammal or inducing osteoblast differentiation in a progenitor cell comprising administering an effective amount of a fusion polypeptide comprising a protein transduction domain and at least one osteoinductive polypeptide, or an osteoinductive polypeptide that has less than 100% homology to LMP-1, RLMP and LMP-1s. (See ps. 5, 12 of the Office Action)

In regard to Nagahara et al., the Examiner stated as follows:

> However, Nagahara et al. do not teach a method of inducing bone formation, wherein an oseoinductve polypeptide has less than 100% homology to LMP-1, RLMP, and LMP-1s. (See ps. 6, 12 of the Office Action).

The Examiner has since changed her mind. Specifically, the Examiner contends that Hair et al. does disclose an isolated osteoinductive region of an LMP-1 protein by disclosing LMP-1s. However, this argument has already been presented and withdrawn. In fact, the Examiner herself acknowledged in the Office Action mailed July 14, 2009 that LMP-1s disclosed in Hair et al. is not an osteoiductive polypeptide comprising at least one isolated osteoinductive region of an LMP-1 protein and having less than 100% homology to LMP-1s, as required by the claims. (See page 3 of the Office Action, Response to Arguments Pertaining to 35 USC 103(a).) The Examiner failed to present any reasons for this sudden reversal of the Examiner's previous conclusions.

The Examiner also argues that Hair et al. teaches the instant SEQ ID NO: 7 which is disclosed in amino acids 120-149 of SEQ ID No: 10 in Hair et al. SEQ ID NO: 10 disclosed in Hair et al. is LMP-1 (See e.g. US Patent No. 6,858,431, claim 10). Because the instant claims specifically require the inventive peptides to include at least one isolated osteoinductive region of an LMP-1 protein, sequences of the inventive peptides in whole or in part would inherently be incorporated in the LMP-1 sequence. This however does not make the invention obvious.

Hair et al. does not teach or disclose specific osteoinductive regions within LMPs. Rather, each of the nucleic acid sequences and protein sequences disclosed in Hair et al. is only contemplated for administration in their entirety and without alterations. There is nothing in Hair et al. that discloses that there are specific region(s) of these genes, rather than the whole gene, that are actually functional for bone formation or that such regions may be specifically isolated and administered in accordance with the present invention. Hair et al. certainly does not teach or suggest administering to a patient one or more of such regions, namely peptides of SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8.

In the example presented in the Office Action, the Examiner picks 29 out of 457 amino acids. Where is the teaching or motivation in Hair et al to select this specific sequence out of hundreds of available alternatives? Could one with ordinary skill in the art at the time of invention reasonably expect from the disclosure of Hair et al. that taking a seemingly random sequence of 29 out of 457 amino acids and administering it to a patient would inducing bone formation, proteoglycan synthesis or osteoblast differentiation? The Examiner fails to explain why would a

person with ordinary skill in the art at the time of invention select this sequence in light of Hair et al, but without the benefit of the instant disclosure. Accordingly, the Examiner has failed to establish that the instant claims are obvious in light of Hair et al. in view of Nagahara et al.

Claims 7-9, 12-15, 21-23, 26-30, 36-38 were rejected as obvious over Boden (Endocrinology 1998, 139(12): 5125-5134) in view of Nagahara et al. and van Beuningen et al. (Osteoarthritis and Cartilage, 1998, Vol. 6, pages 306-317), and in further view of Liu et al. (Bone Miner. Res. 17(3): 406-414 (2002)).

The Examiner again simply recasted an argument from the previous office action. Specifically, the Examiner states that Liu et al. teach LMP-1(t), which is absent evidence to the contrary is different from LMP-1s. (See p. 7 of the Office Action). It has been explained to the Examiner that LMP-1s is not just any shortened LMP-1s, but is a definite short version of human LMP-1. Specifically, LMP-1s refers to a truncated (short) version of HLMP-1, which resulted from a point mutation in one source of a cDNA clone, providing a stop codon which truncated the protein. See e.g., U.S. Patent 6,300,127, Col. 3, lines 17-22. LMP-1s consists of 223 amino acid and is presented in U.S. Patent 6,300,127 as SEQ ID NO: 34. See U.S. Patent 6,300,127, Example 23. Moreover, the Examiner has recognized that LMP-1t of Lie et al. and LMP-1s of Hair et al. is the same protein. (See p. 9 of the office action. "The Examiner agrees that Hair et al. teach a truncated version of LMP-1, and therefore has withdrawn Lie et al. from the rejection."). Applicants respectfully request that the Examiner clarifies her position regarding LMP-1s and LMP-1t.

Because LMP-1s and LMP-1t are the same, Liu et al. is does not teach an osteoiductive polypeptide comprising at least one isolated osteoinductive region of an LMP-1 protein and having less than 100% homology to LMP-1s, as required by the claims. Accordingly, Applicants respectfully request withdrawal of this ground for rejection.

Claims 7-9, 12-15, 21-23, 26-30, 36-38 were rejected as obvious over Boden in view of Nagahara et al. and van Beuningen et al. and Liu et al., and in further view of WO99/06563. WO99/06563 is a foreign counterpart to Hair et al. Similar to Hair et al., it discloses LMP-1 as SEQ ID NO: 10 (see claim 32). As described above, such disclosure is not sufficient to render the instant invention obvious.

In light of the foregoing, Applicants respectfully request withdrawal of this ground for rejection.

2. Double Patenting Rejections.

Claims 7-9 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6858431 ("the '431 patent") in view of Nagahara et al.. Claims 7-9 and 36-38 were also rejected for the same reason over claims 1-13 of U.S. Patent 6,521,750 ("the '750 patent") in view of Nagahara et al. As set forth above, the instant claims are not obvious in light of the '750 patent or '431 patent in light of Nagahara et. al. Claims 7-9 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 10 of U.S. Patent No. 7,504,374 ("the '374 patent").

Applicants respectfully traverse these rejections for the reasons set forth above in regard to the rejections under 35 U.S.C. § 103(a).

3. Rejections under 35 U.S.C § 112

Claims 7-15, 21-30 and 36-40 stand rejected under 35 U.S.C § 112, first paragraph, as failing to comply with the written description requirement. Claims 44-49 are added to the rejection.

The Examiner has not found Applicant's previous arguments persuasive because the specification allegedly does not provide adequate description of the structural and functional relationship of the region that induces proteoglycan synthesis and osteoblast differentiation or have osteoinductive potential. The Examiner also contends that the claimed genus includes sequences that are only 1% homologous and it is unclear how a sequence that is 1% homologous could contain the GAPPPADSA domain.

Initially, it is unclear why this rejection applies to claims 45, 47 and 49. These claims involve a limited genus of polypeptides and the specification supports Applicants' claims that members of this genus induce bone formation, proteoglycan synthesis and osteoblast differentiation. Specifically, the methods claimed in claims 45, 47, and 49 involve polypeptides consisting of a protein transduction domain and a specific amino acid sequence, namely SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8 and combinations thereof. As shown in Fig. 6, introducing these peptides into cells as part of

the fusion protein induces bone growth (Claim 45). From this disclosure, a person with ordinary skill in the art would also understand that introducing these peptides into cells as part of the fusion protein also induces proteoglycan synthesis and osteoblast differentiation (claims 47 and 49).

Moreover, the specification clearly describes the structural and functional relationship of the isolated osteoinductive region that comprises the claimed activity. First, the Examiner argues that SEQ ID NO: 3 does not include the domain GAPPPADSA, but still has osteoinductive potential. The Examiner is respectfully referred to Fig. 6 in the instant specification. As shown in Fig. 6, peptides represented by SEQ. ID. NOs 1-8 have varying degree of osteoinductive activity. For example, introducing into a cell 25 nM of Peptide of SEQ ID NO: 3 results merely in some bone growth, whereas lesser amount of Peptides of SEQ ID NO: 2, SEQ ID NO: 4, and SEQ ID NO: 7 cause higher level of bone growth. Furthermore, although peptides SEQ ID NOs 1, 5, 6, and 8 resulted in similar degree of bone growth as the peptide of SEQ ID. NO 3, much smaller amounts of these peptides were used. Accordingly, peptide of SEQ ID NO: 3 has minimal osteoinductive potential relative to peptides of SEQ. ID. NOs 1-2 and 4-8. Because peptide of SEQ ID NO: 3 does not include the domain GAPPPADSA shared by peptides of SEQ. ID. NOs 1-2 and 4-8, one with ordinary skill in the art would understand that this domain is responsible for higher osteoinductive potential of peptides of SEQ. ID. NOs 1-2 and 4-8.

Second, the Examiner argues that in addition to the domain GAPPPADSA, there are other conserved regions shared among peptides of SEQ. ID. NOs 1-2 and 4-8 and thus it would not be clear to one skilled in the art what sequences should be present. This statement is not accurate. It is true that some peptides share other conserved regions. However, as clearly shown in Exhibit A, the domain GAPPPADSA is the only conserved sequence shared by all peptides of SEQ. ID. NOs 1-2 and 4-8. For example, the Examiner is invited to compare peptides of SEQ ID NO: 1 and SEQ ID NO: 7 or peptides of SEQ ID NO: 1 and SEQ ID NO: 8. One with ordinary skill in the art would know that the domain GAPPPADSA should be present in a polypeptides suitable for use in the claimed methods. Accordingly, the instant specification clearly establishes the structural and functional relationship of the isolated osteoinductive region that comprises the claimed activity.

With respect to the Examiner's argument about the breadth of the claimed genus, Applicants respectfully refer the Examiner to the analysis of claim 1 in Example 9 of the Written Description Training Materials ("Materials"). Claim 1 of Example 9 was drawn to an isolated protein "comprising the amino acid sequence shown in SEQ ID NO: 3." The analysis of that claim notes that even though only a partial structure of a protein is disclosed, one of skill in the art would "recognize that the applicant was in possession of a structural feature shared by all members of the genus." The analysis further goes on to conclude that those of skill in the art would recognize that the applicant would have been in possession of the claimed genus at the time of filing, even though no members of the genus have been described by complete structure.

In this case, the factual scenario is highly similar and the evidence that the written description is satisfied is even stronger, at least because 8 members of the genus of osteoinductive peptides comprising at least one isolated osteoinductive region of an LMP-1 are disclosed in the instant specification. Accordingly, one having ordinary skill in the art would recognize that Applicants were in possession of the claimed genus as Applicants have disclosed a sufficient number of species of the osteoinductive polypeptide comprising at least one isolated osteoinductive region of an LMP-1 genus in combination with description of the structure of the species that is responsible for the osteoinductive functionality of these species.

In light of the foregoing, Applicants respectfully request that the Examiner withdraw this ground for rejection.

CONCLUSION

Applicants believe that they have fully responded to the Examiner's concerns, and the claims of the instant application are in condition for allowance. Applicant respectfully requests that any questions concerning this matter be directed to the undersigned at (901) 396-3133. Please charge any deficiency and/or credit any overpayment to Deposit Account No. 132546.

Respectfully submitted,

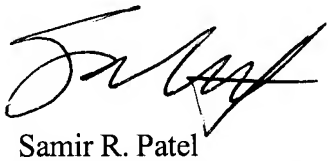

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EXHIBIT A:

SEQ ID 1: APSVSLNKTARPF**GAPPPADSA**

SEQ ID 2: ARPF**GAPPPADSA**PQQNGQPLR

SEQ ID 3: KPQKASAPAADPPRYTFAPSVS

SEQ ID 4: LNKTARPF**GAPPPADSA**PQQNG

SEQ ID 5: ASAPAADPPRYTFAPSVSLNKTARPF**GAPPPADSA**PQQNG

SEQ ID 6: SKPQKASAPAADPPRYTFAPSVSLNKTARPF**GAPPPADSA**PQQNG

SEQ ID 7: **GAPPPADSA**PQQNGQPLRPLVPDASKQRLM

SEQ ID 8: **GAPPPADSA**PQQNGCRPLTNSRSDRWSQMP